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**Longitudinal associations of sauna bathing with inflammation and oxidative stress: The KIHU
prospective cohort study**

Running Title: Sauna bathing, inflammation and oxidative stress

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ABSTRACT

Purpose: We sought to determine cross-sectional and longitudinal associations of frequency of sauna bathing with high sensitivity C-reactive protein (hsCRP), fibrinogen, leucocyte count, and gamma-glutamyltransferase (GGT).

Design: Baseline sauna bathing habits were assessed in 2269 men aged 42-61 years. Concentrations of hsCRP, fibrinogen, leucocyte count, and GGT were determined at baseline and 11 years later. The associations of sauna bathing frequency with baseline and 11-year hsCRP, fibrinogen, leucocyte count, and GGT levels were examined using robust multivariate regression analyses.

Results: In baseline analysis, 4-7 sauna sessions/week (compared with 1 sauna session/week) was associated with -0.84 mg/l (95% CI, -1.55, -0.14; $p=0.019$) lower hsCRP; -0.07 g/l (95% CI, -0.15, 0.02; $p=0.112$) lower fibrinogen; and $-0.28 \times 10^9/l$ (95% CI, -0.51, -0.06; $p=0.015$) lower leucocyte count, after multivariable adjustment. In longitudinal analysis, the corresponding estimates were -1.66 mg/l (95% CI, -3.13, -0.19; $p=0.027$); -0.16 g/l (95% CI, -0.31, -0.02; $p=0.031$); and $-0.49 \times 10^9/l$ (95% CI, -0.85, -0.14; $p=0.007$) respectively. Sauna bathing frequency was not associated with GGT at baseline and 11 years.

Conclusion: Observational evidence supports the hypothesis that reduction in inflammation may be one of the pathways linking frequent sauna bathing with decreased risk of acute and chronic disease conditions.

Keywords sauna bathing; inflammation; oxidative stress; cohort study

KEY MESSAGES

- Cross-sectional evidence or short-term studies suggest Finnish sauna bathing may exert its beneficial health effects via reduction in inflammation and oxidative stress; however, the long-term effects of sauna bathing on these outcomes are uncertain
- In this population-based prospective cohort study, frequent sauna sessions significantly decreased levels of inflammatory markers at baseline and 11-years follow-up; but had no effect on oxidative stress.
- The health benefits of sauna bathing may in part be mediated via reduced systemic inflammation.

Introduction

Sauna bathing, an activity that has been a long-held tradition in Finland and becoming common in other Nordic countries, is a form of passive heat therapy which is mainly used for the purposes of pleasure, wellness, and relaxation. The Finnish sauna is the most popular among all types of passive heat therapy and hence the most widely studied.(1) It is also becoming increasingly popular in many other countries.(2, 3) Beyond its use for pleasure, emerging evidence suggests that Finnish sauna bathing has numerous health benefits. Promising results suggest that sauna bathing may be used for the amelioration of symptoms associated with conditions such as musculoskeletal diseases,(1, 4) headache,(5) common cold, and skin diseases such as psoriasis.(6) Frequent sauna bathing has also been demonstrated to be associated with reduced risks of future cardiovascular disease (CVD),(7) dementia,(8) respiratory conditions,(9, 10) as well as all-cause mortality.(7) There is a need for further research to investigate the mechanistic pathways underlying these associations. Since oxidative stress and systemic inflammatory processes have been implicated in the aetiology of these non-communicable chronic diseases (i.e., individuals with higher circulating concentrations of markers of inflammation and oxidative stress are at higher risk of developing these conditions(11-18)), it has been speculated that some of the pathways by which sauna bathing exhibits its beneficial effects may be via reduction in inflammation and oxidative stress.(7, 19, 20) The effects of other types of passive heat therapy such as Waon therapy, infrared-ray saunas, warm water immersion, and Turkish baths on inflammation and oxidative stress have been reported in several studies.(21-25) A number of studies have also suggested that exposure to Finnish sauna may be associated with alteration in concentrations of essential markers of inflammation and oxidative stress.(26-29) However, these previous findings were however based on short-term effects of sauna exposure or cross-sectional associations. Sutkowy and colleagues demonstrated that a single Finnish sauna bath could reduce the oxidative stress induced by a 30-minute aerobic exercise in healthy men.(26) In a recent study by our group, we showed that the frequency of sauna bathing was inversely associated with baseline levels of circulating serum C-reactive protein (CRP).(27) Given the short-

comings of these previous findings, the temporal nature of the relationship of Finnish sauna baths with inflammation and oxidative stress is unclear. Investigation of the longitudinal relationships of sauna bathing with systemic inflammation and oxidative stress in large-scale observational prospective cohort studies are more informative of the nature of any temporal associations than investigation of associations in cross-sectional studies. Exploring this temporal association may shed light on and lead to better understanding of the mechanistic pathways underlying the health effects of Finnish sauna exposure. In a population-based prospective cohort study comprising of 2269 Caucasian men, we aimed to examine the cross-sectional and longitudinal associations of Finnish sauna bathing with systemic inflammation and oxidative stress as measured by circulating high sensitivity (hs) CRP, fibrinogen, leucocyte count, and gamma-glutamyltransferase (GGT). These markers were chosen given their established roles as markers of inflammation and oxidative stress and in the development of outcomes such as cardiovascular disease outcomes, dementia, and mortality.(11-18)

Materials and methods

We employed the Kuopio Ischemic Heart Disease (KIHD) risk factor study this analysis. Details of study design and recruitment procedures have been described in previous reports.(30, 31) Briefly, the KIHD study recruited a representative sample of middle-aged men aged 42-61 years from Kuopio and surrounding communities in eastern Finland between 1984 and 1989. The study protocol was approved by the ethical committee of the University of Eastern Finland. Assessment of demographic, medical, and lifestyle characteristics including physical activity, collection of blood specimens and biochemical and lipid measurements have been described previously.(32) Baseline sauna bathing habits were assessed by questionnaires which were self-administered and included assessment of the weekly frequency of sauna sessions.(33) Participants were categorized into three sauna bathing frequency groups (1, 2-3 and 4-7 sessions per week). Serum hsCRP was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA) and GGT activity using the kinetic method

(Thermo Fisher Scientific, Vantaa, Finland). Leucocyte counts were determined by Sysmex KX analyzer (Sysmex Co., Kobe, Japan). Plasma fibrinogen concentrations were determined in fresh plasma samples with excess thrombin using the Coagulometer KC4 device (Heinrich Amelung GmbH, Lemgo, Germany). Concentrations of hsCRP, fibrinogen, leucocyte count, and GGT were measured at baseline with repeated measures at 11 years. Participants who did not use sauna at all (n=12) were excluded from the analyses. The associations of sauna bathing frequency with baseline and 11-year hsCRP, fibrinogen, leucocyte count, and GGT levels were examined using robust multivariate regression analyses that took into account age, body mass index, smoking status, history of type 2 diabetes, systolic blood pressure, total cholesterol, history of coronary heart disease, alcohol consumption, socioeconomic status, and leisure-time physical activity. We selected these covariates on the basis of their role as potential confounders and evidence from previous research. All analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

Results

The mean age of study participants at baseline was 53.2 (standard deviation, 5.1) years. Compared to men who had one sauna session per week, participants who had 4-7 sauna sessions per week were slightly younger, more likely to be physically active, less likely to be smokers and have prevalent type 2 diabetes, and had lower levels of inflammatory markers as measured by hsCRP, fibrinogen, and leucocyte count (**Table 1**). In partial correlational analyses that adjusted for age, frequency of sauna bathing (as a continuous variable) was inversely correlated with baseline \log_e hsCRP ($r=-0.07$, $p<0.001$), \log_e fibrinogen ($r=-0.05$, $p=0.011$), and leucocyte count ($r=-0.11$, $p<0.001$), but was not correlated with \log_e GGT ($r=-0.03$, $p=0.128$). Findings of cross-sectional and longitudinal associations of frequency of sauna bathing with circulating hsCRP, fibrinogen, leucocyte count, and GGT are presented in **Table 2**. In cross-sectional analyses, compared to a single sauna session/week, 2-3 and 4-7 sauna sessions/week were

associated with significant decreases in hsCRP levels after adjustment for confounders, -0.68 mg/l (95% CI: -1.15 to -0.21; $p=0.005$) and -0.84 (95% CI: -1.55 to -0.14; $p=0.019$) respectively.

There was evidence of decreases in levels of fibrinogen and GGT, but the associations were not significant. Compared to a single sauna session/week, 4-7 sauna sessions/week was associated with a significant decrease in leucocyte count on multivariate adjustment, $-0.28 \times 10^9/l$ (95% CI: -0.51 to -0.06; $p=0.015$). In longitudinal analyses, the declines in 11-year hsCRP levels for 2-3 and 4-7 sauna sessions/week were -1.26 mg/l (95% CI: -2.36 to -0.17; $p=0.024$) and -1.66 mg/l (95% CI: -3.13 to -0.19; $p=0.027$) respectively. There were also significant decreases in levels of 11-year plasma fibrinogen concentrations and leucocyte counts for 2-3 and 4-7 sauna sessions/week, however, this association was not evident for serum GGT.

Discussion

Using a population-based prospective cohort of middle-aged Caucasian men who had measured levels of biomarkers of inflammation and oxidative stress at baseline and at 11-year follow-up, frequent sauna sessions were associated with decreases in levels of inflammatory markers as measured by hsCRP, fibrinogen, and leucocyte count in cross-sectional and longitudinal analyses. The associations were independent of age, body mass index, smoking status, history of diabetes, systolic blood pressure, total cholesterol, prevalent coronary heart disease, alcohol consumption, socioeconomic status, and physical activity. The declines were however consistent for hsCRP compared to the other inflammatory markers. We have recently demonstrated an inverse cross-sectional association between frequency of sauna bathing and hsCRP.(27) The current findings do suggest that the protective effect of sauna bathing on vascular and non-vascular diseases may in part be mediated via reduced inflammation, as systemic inflammatory processes are well known to be involved in the aetiology of several disease conditions, especially in the development and progression of atherothrombosis.(34) C-reactive protein is the major marker of systemic inflammation which is produced in the liver. Fibrinogen, a major coagulation protein in the

blood and an important determinant of blood viscosity and platelet aggregation, is also an inflammatory marker. Leucocyte count is also one of the major components of the inflammatory pathway. Elevated levels of these markers of inflammation have consistently been shown to be associated with an increased risk of chronic non-communicable diseases such as CVD and dementia as well as all-cause mortality.(11, 12, 16-18) We found no evidence of an association of frequency of sauna bathing with serum GGT, which was used as a marker of oxidative stress, and has been consistently shown to be associated with the risk of CVD, dementia, and mortality.(13-15) The literature on the effect of sauna bathing on oxidative stress has been mostly conflicting. While some previous studies have shown that a single Finnish sauna bath is able to reduce oxidative stress,(26) others have shown that sauna bathing causes oxidative stress.(28) Indeed, it has been shown that the Finnish sauna is a source of reactive oxygen species.(26) Further mechanistic research is warranted to evaluate the impact of sauna exposure on oxidative stress.

Emerging evidence from both observational and interventional studies suggests sauna bathing has great benefits beyond its use for pleasure and relaxation and these include protective effects on several disease conditions. Knowledge of the biological mechanisms (such as reduction in inflammation) underlying the associations between sauna bathing and several disease states justifies the plausibility that the benefits attributed to sauna baths may support a true protective effect. In our recent experimental studies, we have shown that short sauna bathing sessions lead to changes in hemodynamic parameters and improved vascular function,(35, 36) pathways which may explain the protective effects of sauna exposure on vascular disease. Sauna bathing has a good safety profile and its potential as a long-term health intervention deserves further evaluation.

Strengths of the current study include its novelty, the large sample size and inclusion of men who were representative of the general population, long-term follow-up, and availability of data on several potential confounders as well as repeated measures of our outcomes. Limitations include the observational design which precludes the ability to infer causality, lack of generalisation of findings to women, and lack of

data on other relevant markers of inflammation and oxidative stress (such as interleukin-6, interleukin-18, tumour necrosis factor- α , and isoprostanes).

Conclusions

The association observed between frequent sauna baths and decline in levels of several inflammatory biomarkers supports the hypothesis that reduction in inflammation may be the link between frequent sauna bathing and decreased risk of vascular and non-vascular disease conditions. Long-term interventional studies are however required to confirm these findings and assess other potential pathways that underlie the health benefits of regular sauna baths.

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Disclosure of interest

The authors report no conflicts of interest

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Table 1. Baseline characteristics of overall study participants and according to frequency of sauna bathing

Characteristic, unit	Frequency of sauna bathing (sessions/week)				<i>p</i> -value for heterogeneity
	Overall	1	2-3	4-7	
	N=2269	(N=595)	(N=1477)	(N=197)	
	Mean (SD) or median (IQR) or n (%)	Mean (SD) or median (IQR) or n (%)	Mean (SD) or median (IQR) or n (%)	Mean (SD) or median (IQR) or n (%)	
Response variables					
Serum hsCRP, mg/l	1.26 (0.69-2.37)	1.51 (0.72-2.90)	1.22 (0.68-2.29)	1.21 (0.75-2.05)	< 0.001
Plasma fibrinogen, g/l	2.96 (2.63-3.33)	3.03 (2.69-3.43)	2.93 (2.61-3.31)	2.91 (2.62-3.21)	0.004
Leucocyte count, x 10 ⁹ /l	5.65 (1.56)	5.82 (1.76)	5.61 (1.48)	5.34 (1.48)	< 0.001
Serum GGT, U/L	20 (15-33)	22 (15-36)	20 (14-31)	21 (15-34)	0.007
Characteristics, unit					
Age, years	53.2 (5.1)	53.5 (5.0)	53.3 (5.04)	51.5 (5.7)	< 0.001
Body mass index, kg/m ²	26.8 (3.5)	26.9 (3.6)	26.7 (3.4)	27.8 (4.2)	< 0.001
Alcohol consumption, g/week	31.0 (6.3-89.0)	31.0 (6.6-94.1)	30.0 (6.1-86.6)	39.0 (7.1-112.0)	0.048
Serum total cholesterol, mmol/l	5.90 (1.08)	5.87 (1.10)	5.93 (1.08)	5.81 (1.02)	0.280
Systolic blood pressure, mmHg	134 (17)	135 (18)	133 (16)	135 (17)	0.054
Diastolic blood pressure, mmHg	89 (10)	89 (11)	88 (10)	90 (11)	0.070
Leisure-time physical activity, kJ/day	1215 (655-2005)	1115 (563-1830)	1236 (681-2038)	1428 (678-2202)	0.010
Socio-economic status	8.41 (4.25)	8.69 (4.29)	8.37 (4.22)	7.83 (4.32)	0.041
Clinical Conditions					
Smokers	699	212	447	40	< 0.001
History of type 2 diabetes	88	30	56	2	0.038
History of coronary heart disease	552	154	361	37	0.130

hsCRP, high sensitivity C-reactive protein; GGT, gamma-glutamyltransferase; IQR, interquartile range; SD, standard deviation

Table 2. Cross-sectional and longitudinal associations of frequency of sauna bathing with markers of inflammation and oxidative stress

Frequency of sauna bathing (sessions/week)	Cross-sectional association (Baseline)		Longitudinal association (11-year follow-up)	
	Mean difference (95% CI)	P-value	Mean difference (95% CI)	P-value
<i>Serum high sensitivity C-reactive protein (mg/l)</i>				
1	referent		referent	
2-3	-0.68 (-1.15 to -0.21)	0.005	-1.26 (-2.36 to -0.17)	0.024
4-7	-0.84 (-1.55 to -0.14)	0.019	-1.66 (-3.13 to -0.19)	0.027
<i>Plasma fibrinogen (g/l)</i>				
1	referent		referent	
2-3	-0.05 (-0.11 to 0.00)	0.054	-0.12 (-0.23 to -0.00)	0.047
4-7	-0.07 (-0.15 to 0.02)	0.112	-0.16 (-0.31 to -0.02)	0.031
<i>Leucocyte count ($\times 10^9/l$)</i>				
1	referent		referent	
2-3	-0.12 (-0.27 to 0.02)	0.085	-0.31 (-0.58 to -0.04)	0.025
4-7	-0.28 (-0.51 to -0.06)	0.015	-0.49 (-0.85 to -0.14)	0.007
<i>Serum gamma-glutamyltransferase (U/L)</i>				
1	referent		referent	
2-3	-3.19 (-6.89 to 0.51)	0.091	-0.54 (-5.36 to 4.27)	0.826
4-7	-3.74 (-10.10 to 2.63)	0.250	14.15 (-5.89 to 34.18)	0.166

CI, confidence interval

All analyses were adjusted for age, body mass index, smoking status, history of diabetes, systolic blood pressure, total cholesterol, prevalent coronary heart disease, alcohol consumption, socioeconomic status, and leisure-time physical activity